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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,467	12/11/2001	Walter Sebald	086033-000000US	2473

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EXAMINER	
ANDRES, JANET L	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,467	SEBALD, WALTER	
	Examiner	Art Unit	
	Janet L. Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 11-26* is/are rejected.

7)☒ Claim(s) *3 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/01,1/03,4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of SEQ ID NO:1 in the reply filed on 1 July 2004 is acknowledged. The traversal is on the ground(s) that there is a common structural feature at X1, X4, and X6 and because the cited documents do not teach increased heparin binding. This is not found persuasive because the common structural elements are selected from the group of lysine, histamine, and arginine, each of which is known in the art. Furthermore, heparin-binding sequences are taught by the prior art, as stated in the restriction requirement, and increased heparin binding would result from incorporation of such sequences into a polypeptide. Additionally, heparin-binding sequences within the scope of Applicant's generic claims, which presumably have the characteristics claimed by Applicant, are also known in the art; see below. The election of species with respect to the BMP family is withdrawn since BMPs and their functions are well known in the art.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-26 are pending in this application and currently under examination as they relate to SEQ ID NO: 1.

Claim Objections

Claims 1, 2, 4-9, and 11-26 are objected to because they encompass non-elected inventions.

There is a typographical error in claim 20.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 16 recites " a host cell", which encompasses the host cell as it occurs in nature, for example, as a gene therapy patient. However, since Applicant does not intend to claim naturally occurring products amendment of the claim to show the hand of man would obviate this rejection. It is suggested that claim 10 be amended to recite "an isolated host cell...".

Claim 24 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-7, 9, and 11-26 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. patent application publication 2002/0020086 A1 (priority date August, 1998).

The '086 publication teaches the heparin-binding domain CKRKCN, which comprises instant SEQ ID NO: 1 (p. 2, column 2, table 1). The publication further teaches that fusion

proteins can be made in any growth factor using such heparin binding domains in paragraph 11. N-terminal fusion is taught also taught in paragraph 11, as are encoding sequences and recombinant expression, including expression by bacteria and purification. Histidine tagging is taught in paragraph 86. The '086 publication teaches variants of growth factors in paragraph 14. Since the publication teaches N-terminal addition and CTGF, it also teaches incorporation before a cysteine knot. Since many of the proteins set forth in paragraph 14 are dimers, it further teaches the dimers of claim 11. Pharmaceutical compositions for wound healing are also taught in paragraph 14. Attachment to heparin is taught in paragraph 12; compositions comprising CTGF or transforming growth factor β as taught in paragraph 14 would be osteinductive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4-7, 9, and 11-26 are also rejected under 35 U.S.C. 103(a) as being unpatentable over the '086 publication in view of U.S. patent 5,652,332. The '086 patent teaches

as set forth above but teaches no other peptides within the scope of the instant claims. The '332 patent teaches heparin-binding sequences that comprises instant SEQ ID NO: 1 (BPI.2 and BPI.3; see figure 16 and column 10). It would be obvious to the artisan of ordinary skill to combine the teachings of the '086 publication with those of the '332 patent to use BPI2 or BPI3 to form heparin-binding variants. One of ordinary skill would be motivated to do so because the '086 application teaches uses for such variants, and the '332 patent teaches alternative peptides that would be expected by the artisan to also function for the same purposes.

Claim 8 is rejected under 35 U.S.C. 103(a) as unpatentable over the '086 publication in view of Linkhart et al. (Bone, 1996, vol. 19(1 suppl): 1S-12S).

The '086 application teaches as set forth above but fails to teach BMPs. Linkhart et al. teaches that BMPS are related to transforming growth factor β and that they are osteoinductive, and thus useful for bone healing (pp. 5S-6S). Linkhart et al. further teaches the need for matrices in order to use these BMPs (p. 5S). It would be obvious to one of ordinary skill in the art to combine the teachings of the '086 application with those of Linhart et al. to modify BMPs with heparin binding sites so that they could be used with matrices such as heparin and fibrin. One of ordinary skill would be motivated to do so because the '083 patent teaches ways of modifying growth factors so that they may be attached to matrices, and Linkhart et al. teaches that such an attachment is useful for BMPs. Thus one of ordinary skill would expect improved bone healing from BMPs modified as taught by the '086 application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-9, and 11-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for variants comprising the peptides RKRA and RKRAKHKQ, as well as those disclosed by the prior art, does not reasonably provide enablement for all peptides meeting the limitations of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to compositions and methods requiring sequences comprising a generic sequence in which no amino acid is uniquely specified, and in which only five are required, of which two can be any of three possibilities, and three can be any of twenty three possibilities. Thus the claims are very broad, encompassing sequences that need not have a single residue in common. Applicant has described two sequences meeting structural limitations of the claims that have heparin binding activity, and the art teaches three more. As opposed to the claims, then, what is disclosed about the heparin-binding sequences is narrow: two peptides, and the three taught by the art. There is no guidance in the specification to indicate that these peptides are correctly described by Applicant's generic sequence, so that the artisan could

predictably use other members of the genus to increase heparin binding of polypeptides. The other sequences disclosed by the prior art do not have even the loosely defined features of Applicant's SEQ ID NO: 1 (see the '086 application and the '332 patent). Thus neither the prior art nor the instant specification provides sufficient guidance to indicate members of the claimed genus could predictably be used to bind heparin.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of peptides that bind heparin, and the lack of direction or guidance for using peptides that are not identical to those already shown to function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claim 7 additionally lacks enablement for proteins with alterations, additions, substitutions, insertions, inversions, and/or deletions, with no limitation as to structure and no functional limitation other that that the encompassed proteins maintain the "biological activity" of the original molecule. This claim encompasses a potentially infinite number of variations to undefined proteins, with no particular activity required. The specification provides no guidance as to how such a large number of unrelated proteins with unrelated functions could be made and used. Thus, without further guidance, it would require undue experimentation for the artisan to make and use such proteins as broadly claimed.

Claim 9 lacks enablement for placement of the heparin-binding residue before the cysteine knot, since not all proteins have cysteine knot.

Claims 24-26 lack enablement commensurate in scope with the claims since the artisan could not predictably use all variants within the scope of the claims for wound healing or other treatments; claim 1 encompasses modifications to all proteins.

Claims1, 2, 4-9, and 11-26 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus in which no residues are uniquely required, as stated above. The members of this genus thus vary substantially in length and in composition, and could have very different structural and functional characteristics from the two sequences disclosed and the three taught in the art. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Since there are no required common regions, no impart characteristic physical, structural or functional features are imparted to the invention. The skilled artisan thus cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the method of isolation. There is no guidance in the specification or in the prior art to indicate that the very limited common features of the claimed genus are sufficient to impart the characteristics function. The subject matter is not sufficiently described so as to indicate to the artisan that Applicant is in possession of a genus of heparin-binding peptides.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrases "such as" and "preferably" render the claims indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. See MPEP § 2173.05(d).

Claim 24 provides for the use of a polypeptide variant, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Allowable Subject Matter

Claims 3 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

CLAIMS 3 AND 10 ARE OBJECTED TO. CLAIMS 1, 2, 4-9, AND 11-26 ARE REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Andres whose telephone number is 571-272-0867. The examiner can normally be reached on Monday, Tuesday, Thursday, Friday, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Andres, Ph.D.
27 September 2004

JANET ANDRES
PRIMARY EXAMINER